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Abstract

One of the most revealing parts of the human body is the eye. In fact, systemic conditions and diseases are commonly manifested in the eye and display pathology that reflect disorders. An example of a chorioretinal vascular condition that can present itself in the eye is diabetes mellitus, which if left uncontrolled can damage the eyes and a person's vision. Age related macular degeneration is specific to the eye, potentially leading to irreversible loss of central vision. Intravitreal injections containing vascular endothelial growth factor inhibiting agents appear to be the leading lines of defense against diabetic retinopathy and macular degeneration progression, helping to reduce both the pathological and visual manifestations of these chorioretinal vascular diseases.

Background

Diabetes is the fourth leading cause of health complications, making many people susceptible to diabetic retinopathy. In fact, the prevalence of diabetes is expected to increase by 7.7% by 2030, leaving many people at risk (Abbas et al., 2017). Age related macular degeneration is another neovascular condition of the eye which can reduce visual acuity to 20/800 in a patient's better eye by 60%, resembling a patient who "is bedridden with a catastrophic stroke" (Folk & Stone, 2012). These diseases are capable of impairing the daily functioning of a patient if they are not treated and monitored. Most ocular diseases can be identified with a dilated eye exam. Treatments with delivery of vascular endothelial growth factor inhibitors to the retina via intravitreal injection has gradually become the first line of treatment for ocular conditions such as diabetic retinopathy and macular degeneration. Pan-retinal photocoagulation (PRP) is a laser treatment that can also be used in controlling these conditions and preventing the progression of vision loss. Research is currently being done on both of these methods in an effort to determine their use in ocular disease.

Hypothesis

In most circumstances, vascular endothelial growth factor inhibiting medications can be implemented in a treatment plan to alleviate both the visual complaints and the pathological findings associated with chorioretinal vascular conditions. In some cases, however, this treatment option may not be appropriate due to potential risks and another treatment may be indicated.

Methods

Research for this paper was conducted with the use of ProQuest, EBSCO, and Pub-Med databases. Figures used throughout include corresponding sources from research articles.

Diagnostic Methods

Conditions such as age-related macular degeneration and diabetic retinopathy can be diagnosed with a proper exam. Ophthalmic tropicamide, a mydriatic, is used in order to give the clinician a proper view of the fundus. Imaging methods such as optical coherence tomography (OCT), fluorescein angiography, and wide field fundus imaging may also be used for future comparison during treatment. Diagnostic guidelines have been established to aid in classifying the type and severity of ocular disease. Findings, diagnostic methods, visual complaints, and prognosis of these conditions will be discussed in the following sections. Popular treatment options will also be outlined.

Diabetic Retinopathy

Diabetic retinopathy (DMR) is a complication resulting from diabetes mellitus Type 1 or 2. It appears to be one of the leading causes of blindness in patients aged 20-65 (Stewart, 2012). Currently, 336 million people suffer from diabetes and are therefore at risk of developing diabetic retinopathy, otherwise known as DMR (Abbas et al., 2017). Diabetic damage to the eye is a result of macular edema, which in more advanced cases, can lead to intraocular bleeding, detachments of the retina, macular ischemia, and retinal neovascularization. Possible risk factors for DMR include hyperglycemia, elevated blood pressure, and elevated serum levels (Buffolino & Park, 2019). Patients can usually control risk factors with lifestyle modifications including diet and exercise, yet it is important to note that specific patient demographics can predispose people to diabetic retinopathy.

Firstly, individuals diagnosed with diabetes at an earlier age tend to be more vulnerable to developing the condition. DMR becomes more prevalent as the age of diabetes onset is younger. "What is hitherto unknown is whether the increased prevalence of complications associated with early-onset disease is simply a consequence of the longer duration of disease, a consequence of a more severe metabolic phenotype, or in fact something specific to the diabetic milieu in younger patients that makes tissues more inherently susceptible to hyperglycemic damage" (Wong et al., 2008). Long-term exposure to elevated blood glucose levels seems to lead to oxidative stress on the eyes (Stewart, 2012). By the same token, retinopathy is not common in the first five years of a Type 1 diabetes onset, and diabetic retinopathy tends to be present after 20 years of having Type 2 diabetes (Cook et al., 2008).

Secondly, in addition to patient age, ethnicity is also associated with DMR. African Americans, Hispanics, and South Asians are especially prone to diabetic retinopathy. African Americans seemingly have reduced glycemic control, which can lead to retinal complications due to higher A1C values. The internationally recognized mark differentiating safe and unsafe A1C values is 7% (Long et al., 2017). A study showed that over a six-year period, 72% of African Americans with Type 1 diabetes mellitus developed retinopathy (Buffolino & Park, 2019). Furthermore, the combination of male sex, African American ethnicity, duration of standing diagnosis, and value of hemoglobin A1C, were "positively associated with retinopathy severity" (Long et al., 2017).

Before any signs of diabetic damage appear on the retina, choroidal vessels may constrict due to hypoxia and vascular changes can develop. Furthermore, it is important to note that in the early stages of damage to the retina, the patient may not be able to discern changes in visual acuity; the condition is usually diagnosed in a later stage of diabetic retinopathy (Wang & Tao, 2019). About 50% of patients with diabetes do not come for yearly screening visits (Buffolino & Park, 2019). The first markers of diabetic damage in the eye are the results of swelling and leakage of blood vessels because of poorly controlled blood sugar levels. The natural synthesis of vascular endothelial growth factors (VEGF) results in the disruption of the blood-retina barrier that leads to the spread of serum proteins leading to edema (Stewart, 2012). Bleeding near the macula can noticeably blur the patient's vision. According to Mayo Clinic's webpage on diabetic retinopathy (n.d.), the patient may also complain of fluctuating vision. This can occur because of uncontrolled blood sugar levels that cause the lens to swell and alter the refraction of light in the eye. Two other common visual complaints are impaired color vision and floaters (Vien, n.d.). Over time, the body may begin to generate new blood vessels in order to properly supply the eye with oxygen, which severely impacts the patient's vision and everyday functioning. Other lesions associated with diabetic retinopathy such as microaneurysms, hemorrhages, cotton wool spots, and hard exudates can be seen.

Diagnosis and Prognosis of Diabetic Retinopathy

Diabetic retinopathy is classified into either proliferative or nonproliferative diabetic retinopathy (PDR/NPDR) and then further broken down into mild, moderate, and severe. This classification considers the degree of damage present on the retina. The job of the clinician is not an easy one to classify the stage of diabetic retinopathy. With the help of wide field fundus imaging, the ophthalmologist is able to document and compare any changes to the appearance of the retina. The wide field images below can demonstrate the classifications of diabetic damage to the retina based on any associated findings.

Additionally, optical coherence tomography (OCT) is used to provide cross-sectional scans of the retina which can also help in determining the presence and degree of edema or cotton wool spots. Layers of the retina such as the RPE and choroid may also be altered.

Age-Related Macular Degeneration

Age related macular degeneration (AMD) is the most common cause of blindness in patients older than age 65. In industrialized countries, blindness due to AMD had a reported 1.47% prevalence and affected 1.75 million people in the United States alone (Eng, et al., 2019). The deposition of yellow, extracellular material underneath the retinal pigment epithelium that form drusen, indicative of photoreceptor cells that are degenerating is a key component of AMD (Virgili et al., 2015). The RPE must reuse materials in order to help revitalize photoreceptors. A defect in the cycle suggests the poor quality of enzymes that are responsible for breaking down those materials (Sarks et al., 1994), leading to degeneration of the RPE as drusen evolve into geographic atrophy. Extracellular deposits or atrophy of the RPE near the retina can lead to significant loss of central vision. As the drusen degenerate, they give a white appearance to the retina with "irregular margins and foci of calcification before disappearing to leave a focal patch of atrophy" (Sarks et al., 1994). Most patients complain of blurred or distorted vision or a scotoma (Cook et al., 2008). Risk factors for AMD include smoking, hyperlipidemia, and hypertension. Age-related macular degeneration is also strongly tied to a genetic predisposition to the point that children and siblings of patients with AMD are automatically considered suspects for the condition. Many sources rank genetics as an important contributor to the likelihood of developing age-related macular degeneration. Various studies show that people of African descent have a reduced risk for AMD, than does the Caucasian population (Delcourt, n.d.). Smoking increases the risk of AMD as well.

Although much about AMD and its pathogenesis is still unknown, studies show "that the largest single genetic factor contributing to AMD is a variant of codon 402 in the gene encoding complement…[that] strongly supports the long-held belief that the immune system is an important contributor to AMD" (Folk & Stone, 2012). In some observed cases of AMD, inflammatory mediators and other molecules have been found at the macula, indicating that there is indeed a connection between the condition

and inflammation. Furthermore, the release of excess activated macrophages in chronic inflammatory diseases is linked to cellular damage at the macula. Electron microscopy and immunohistochemistry methods were used to detect the presence of inflammatory biomarkers at sites of atrophy and neovascularization in patients with AMD (Cachulo & Costa, 2017).

Prognosis and Classification of AMD

Age-related macular degeneration is diagnosed with a dilated retinal examination. Evaluating a case of AMD requires paying attention to changes at or near the macula. Age-related macular degeneration begins with the dry form, characterized by the presentation of drusen. Number, size, and location of drusen are helpful in determining the progression of the condition. Additionally, drusen with indistinct borders seem to be indicative of the advancement of AMD (Cachulo & Costa, 2017).

As AMD progresses, the retinal pigment epithelium layer begins to show signs of atrophy. A case of AMD is characterized as wet or neovascular once new blood vessels begin to grow over or underneath the RPE (Folk & Stone, 2012). The generalized term "late AMD" refers to two specific presentations on the macula with exudates which can either be geographic atrophy or vascular AMD. Progression from dry to wet AMD occurs for 15% of patients complaining of severe loss of central vision and presenting with geographic atrophy that develops (Eng et al., 2019). Patients may notice visual distortion of straight lines. Ten percent of patients with AMD suffer from this more advanced form. More than 200,000 patients in the United States alone are diagnosed per year, accounting for 90% of all severe vision loss (Stewart, 2012). In a large study done, "the prevalence of large drusen increased from about 1.5% in Caucasians aged 40-49 years, to more than 25% in those aged 80 years or more" (Delcourt, n.d.). This statistic is important to consider because it indicates that Caucasians appear to be more at risk for developing AMD than people of other demographics such as Hispanic American, African American, and Chinese (Delcourt, n.d.). Of course, as the name of the condition suggests, the likelihood of developing AMD increases exponentially with age.

VEGF in Ophthalmology

Angiogenesis is a process that can be both lifesaving and necessary, yet in some cases can be detrimental. Throughout the body, the natural process for generating new blood vessels is crucial for maintenance related to growth (embryonic or otherwise) and repair. Yet in circumstances of hypoxia and inflammation, it allows the growth of tumors and is linked to the destruction of tissue (Stewart, 2012). Angiogenesis is also important when neovascularization is required such as after myocardial infarction. However, in ophthalmic cases, the generation of new blood vessels can lead to hyperpermeability that can harm vision by leading to retinal detachments and edema between the retinal layers. The primary molecule that is associated with angiogenesis is vascular endothelial growth factor. "Within the posterior segment of the eye, VEGF is produced by retinal pigment epithelial cells, neurons, glial cells, endothelial cells, ganglion cells, Muller cells, and smooth muscle cells" (Stewart, 2012). The primary cells of interest leading to the harms from AMD and DMR however, are vascular endothelial cells. Generally, the synthesis of VEGF is triggered by tissue hypoxia that can either be caused by "primary vascular occlusive disease or anaerobic tumor metabolism" (Stewart, 2012). The mechanism leading to the proliferation of vessels is complex but it results in mitosis and swelling of the endothelial cells, as well as vasodilation, helping new blood vessels develop. Specifically, VEGF works to encourage growth along the endothelial cells and dissolve the spaces between them, leading to the breakdown of the blood-retinal barrier that makes capillaries leak and new, potentially detrimental, blood vessels form (Stewart, 2012). VEGF-A, a subfactor of this molecule, is linked to growth and permeability of newly-developing blood vessels. VEGF inhibitors block the receptors that natural VEGF would bind to, preventing angiogenesis. "Long-term blockade of VEGF-A [receptor] causes shrinkage and maturing of the vessels so that they no longer leak. The accumulation of fluid within and beneath the retina dissolves, and the photoreceptors reattach to the underlying retinal pigment epithelium" (Folk & Stone, 2012). By using a medication that reduces the permeability of the retinal vessels and stopping their growth, leakage is also reduced, preventing swelling in order to bring the patient's visual acuity back to baseline (Folk & Stone, 2012). It is interesting to note that these drugs are capable of resolving findings associated with two very different conditions in that one is systemic and can target multiple parts of the body, while the other is localized in the eye.

VEGF Inhibitors: A Comparison

Although all VEGF inhibitors prevent neovascularization, there are several subclasses of this drug. Their generic names aflibercept, bevacizumab, and ranibizumab will be used throughout this paper (Folk & Stone, 2012). The efficacy of the medications as they compare to each other is still being studied.

Bevacizumab received approval from the Food and

Drug Administration for the treatment of colon cancer. Bevacizumab also binds to VEGF-A, which led clinicians to think that the drug may also be effective in treating neovascularization and exudates on the retina. Although there is no FDA approval for its intravitreal use, bevacizumab is proving itself effective (Folk & Stone, 2012). When compared to other medications in its class, bevacizumab has a longer half-life. One dose of the drug can reduce levels of natural VEGF in the blood by 117 times in just one day and when measured after one month, still maintained a four-fold reduction (Stewart, 2012). Furthermore, many clinicians recommend this drug because of its vast difference in cost compared to others. Being prepared in larger doses than is necessary for the eye means that the medication can be divided for multiple doses (1.25 mg. on average), reducing the cost even further. Whereas a dose of ranibizumab costs $2000, bevacizumab, although regarded as off label therapy, costs $75 per treatment (Folk & Stone, 2012).

Ranibizumab was developed specifically for use in the eye by fragmenting the bevacizumab molecule for higher affinity by five to twenty times more than bevacizumab (Stewart, 2012). A study looking at regular monthly treatment with ranibizumab shows that the first five years of treatment produce the best results in terms of visual acuity, but then results seem to approach baseline levels over time thereafter (Nishikawa et al., 2019). For treatment with ranibizumab, the MARINA study attempted to determine effective dosage of the medication. At random, 716 patients with neovascular AMD were treated with monthly 0.3mg or 0.5mg injections of the drug, or sham treatment for 24 months. Results showed that 92% of patients that were treated with 0.3mg of ranibizumab and 90% treated with 0.5mg lost less than 15 letters when being tested for changes in visual acuity. Furthermore, 26.1% of patients that were treated with 0.3mg and 33.3% with 0.5mg treatment had a 15-letter improvement or greater.

When aflibercept is compared to the other drugs, its increased binding affinity to VEGF-A receptors combined with its larger molecular size allows for a higher efficacy and hence, less frequent treatment. When used on a two-month basis after three monthly consecutive loading doses, results compared to monthly treatment with ranibizumab (Stewart, 2012). Patients with neovascular AMD who were treated with aflibercept intraocular injections were able to sustain improved vision for four years. Even though after one year some regression was present, 94.5% of patients still had improved vision. "Thus, visual gain [of aflibercept] in the first year is generally favorable, but long-term outcome is not as promising" (Nishikawa et al., 2019).

Conclusively, visual acuity was shown to improve with all three classes of treatment, but specific data was shown by a study conducted by DRCR.net in which 600 Americans with diabetic edema participated. The average age was 61 and most people had diabetes for over 15 years. Visual acuity before the study was 20/32 or worse and patients were administered either of the three drugs at random and monitored on a monthly basis in the first year of the study. When comparing the visual acuity of patients after treatment, those on aflibercept for two years were able to read 3.5 more lines compared to ranibizumab patients who read 3, and bevacizumab patients read 2.5 (Wells, 2016). Aflibercept showed better efficacy after the one- and two-year mark. "By two years, 41 percent of participants in the aflibercept group received laser treatment to treat their macular edema, compared with 64 percent of participants in the bevacizumab group and 52 percent in the ranibizumab group." Ultimately, with treatment involving any of the three drugs, visual acuity was improved to 20/32 and 20/40. There were even studies showing the efficacy of bevacizumab in improving patients' visual acuity from 20/235 to 20/172. The results of the study suggest that there is a slight difference between the frequencies at which the drug must be readministered depending on the specific type of medication chosen. According to the DRCR study done, there was no significance to using one medication over another for treatment of mild macular edema when visual acuity is 20/40 or better. However, in cases of 20/50 or worse vision it has been shown that Eylea (aflibercept) performed better than ranibizumab and bevacizumab (Wells, 2016).

Risks

Although this modality of treatment is usually the first line of defense against further damage to the retina, existing risks should be considered. Firstly, for all the subclasses of intravitreal injections used for treating chorioretinal disorders, the risk for eye infection and inflammation is the same. These are consequences of the administration and not the drug itself (Wells, 2016). Injection into the vitreous chamber also raises the risk for endophthalmitis, retinal tear or detachment at the area of injection, and vitreous hemorrhage because of penetrative trauma (Pershing et al., 2013). These risks must be kept in mind when developing a treatment plan for a patient suffering with other kinds of ocular disease as well. Furthermore, because additional fluid is added to the vitreous cavity when the medication is given, an elevation in intraocular pressure from increased volume in the eye can result.

A study was done spanning academic centers Stanford University Hospital & Clinics and Mayo Clinic. Patients who received anti-VEGF injections between January 1,

2006 and December 31, 2010 participated in order to determine the relationship between administration of the drug and intraocular pressure elevation taking place within 60 days of the injection. Intraocular pressure asymmetry between the eyes by a value of more than 3mm Hg was also considered. Those with a history of glaucoma or elevated IOP in the past did not qualify to participate. "A total of 11,828 bevacizumab injections and 10,354 ranibizumab injections were administered during the study period at the two clinical sites. In this series, 21 eyes of 18 patients developed elevated IOP of 24mm Hg of higher within 60 days of previous injection" (Pershing et al., 2013). Most patients were Caucasian females who received treatment for wet AMD and presented other pathology related to elevated IOP, such as narrow anterior chamber angles on gonioscopy. Most of the 21 eyes needed treatment for elevated pressure, 76% required prolonged treatment, and 19% resolved with no treatment. It was found that a risk of increase in IOP persisted even later in treatment after multiple injections to the eye. This risk was reported regardless of the subclass of anti-VEGF used, however a higher chance of IOP elevation in ranibizumab treatment was reported (Pershing et al., 2013). This risk is especially important to consider if the patient in question has glaucoma or is a glaucoma suspect, as a subtle rise in intraocular pressure may be detrimental. In such a case, the drug should be administered and the patient carefully monitored for changes in IOP that may lead to an acute attack of glaucoma.

Additionally, receiving anti-VEGF drugs alongside having coexisting cardiovascular conditions may lead to adverse effects. The SUSTAIN trial showed that although there is no link to myocardial infarction, a 10% incidence of stroke was found in patients with previous cerebrovascular disease that were also being treated with VEGF inhibiting medications (Stewart, 2012). In patients receiving regular treatment with ranibizumab, there was a higher incidence of heart attack, stroke, or death from cardiovascular or unknown conditions (Wells, 2016).

Finally, the nature of this treatment option for AMD/DMR is that frequent, monthly follow up visits are required to monitor and readminister the drug, rendering compliance of treatment more difficult to upkeep. Inherent drawbacks to the use of VEGF inhibiting agents are its cost and frequency of treatment as it relates to burden on the patient. Perhaps lowering the overall cost of the treatment (medication and visit) while creating a medication with a longer half-life or efficacy will allow more patients to undergo long term treatment, preventing blindness (Baek et al., 2019). In some cases, the use of a laser to clear drusen and prevent the furthering of neovascularization may be more appropriate, as will now be discussed.

Use of Pan Retinal Photocoagulation

Although traditional cases of diabetic retinopathy and macular degeneration now indicate treatment with intravitreal injections, this has not been the case for long. In the past, the first line of defense was treatment with blue-green Argon laser in order to create lesions around the area of retinal neovascularization and promote the regression of abnormal blood vessels and drusen. This option to help DMR and AMD is called pan retinal photocoagulation. In this technique, a beam of light from the laser is focused onto the retina using a special lens. The strength of the laser now used is usually weaker, with studies trying to determine the efficacy of subthreshold laser treatment to avoid applying more energy than necessary. Up to 300 lesion spots may be delivered, with each one between 100μm and 200μm in size. "Subthreshold photocoagulation delivers light energy with very short impulses that are absorbed by the RPE only, aiming to spare the neurosensory retina". Adjusting the strength, pulse duration, and frequency of the laser makes the treatment effective yet more gentle on the choroid in an attempt to reduce potential photoreceptor loss. Although the mechanism of treatment is not fully known, some ideas explain its efficiency.

Firstly, the laser may help in clearing remnants left by phagocytic cells and macrophages along the choroid. It is hypothesized that the accumulation of these cells leads to the development of drusen. Another train of thought is that the laser may precipitate the RPE layer to release cytokines and growth factors that are able to "modify the biochemical processes underlying the clinical manifestations of the retinal disorder, rather than simply destroying drusen, and may also act on the drusen remote from the site of laser energy application" (Virgili et al., 2015). Also, the laser energy is capable of causing the temperature of the retina to rise slightly, leading to the release of heat shock proteins. They "act as chaperones for refolding misfolded proteins in aging cells, thereby rejuvenating retinal pigment epithelium (RPE) cells and restoring their cellular function" (Eng et al., 2019).

A study included patients with extrafoveal neovascular presentation with drusen. Patients were 50 years of age or older and visual acuity either was 20/100 or worse (Silva, 2011). The laser used was a conventional blue-green Argon laser. Energy was set to be powerful enough to create the necessary lesions or controlled burns on neovascular areas. In this study, attention was not paid to maintaining sub-threshold energy. By using pan retinal

photocoagulation, the likelihood to stabilize the visual acuity of a patient doubled for those eyes, showing a 58% reduction in the risk to have severe vision loss.

Highlights from the Macular Photocoagulation Study Group (Silva, 2011) are shown here:

A. Five years after treatment, average visual acuity was 20/125 in the group treated compared to 20/200 in patients not treated with PRP.
B. Within the five-year span of treatment, 54% of patients had signs of recurring severe vision loss, with the majority of cases taking place within two years of treatment.
C. Smoking after PRP treatment was linked to accelerated recurrence of severe vision loss, as 85% of patients smoked more than 10 cigarettes per day compared to 51% in the non-smoking population.

An additional analysis of 12 studies of 2,481 eyes that were treated with subthreshold pan retinal photocoagulation showed similar results. This study included treatments done with 514nm and 810nm lasers. Conclusions of the review showed that pan retinal photocoagulation treatment is effective in reducing drusen count and thereby improving visual acuity in patients with dry AMD with the 810nm laser being consistently more effective. However, the study mentions that in order to obtain a significant improvement in visual acuity, the treatment must clear a substantial amount of drusen. Additionally, the study found that among the eyes that were treated, there was "no significant change in the risk of developing choroidal neovascularization or geographic atrophy" (Eng et al., 2019) and that more research would need to be done to conclusively confirm the efficacy of the 810nm infrared diode laser compared to the 514nm laser.

Comparing the treated patients with the observed patients in the study, the following data was obtained in regard to the relationship of diminishing drusen and treatment with pan retinal photocoagulation (Eng et al., 2019):

1. In five out of the 12 studies in which visual acuity was measured, it was determined that there was no difference in visual acuity in the groups who had and had not received treatment. Yet, the remaining studies showed a correlation between receiving treatment and improved visual acuity. This indicates that although pan retinal photocoagulation may be effective in clearing drusen from the retina, perhaps more research is necessary to conclude the effectiveness of the laser in improving the visual outcome for the patient.
2. In regard to the development of choroidal neovascularization (CNV), three of nine studies that followed up on this mentioned that there was no development of CNV. An additional three however noted that eyes treated with subthreshold pan retinal photocoagulation were slightly more likely to develop CNV.
3. Geographic atrophy was also monitored in this series of studies. It was reported that two studies showed GA in treated eyes, while another study showed that although the incidence of developing geographic atrophy in treated eyes was 3.9%, the likelihood was higher in eyes that were not treated, at 14.0%.

After five years, following up on patients showed 64% of eyes that were not treated with the laser developed more severe vision loss compared to 46% of patients that had treatment with PRP. Yet, the recurrence rate of vision loss was 54%, with 75% of those recurrences taking place in the first year (Cook et al., 2008).

Conclusion

Currently, there are a number of available treatment options to reduce visual complaints and pathological findings in patients with chorioretinal vascular conditions. Interventions such as subthreshold pan retinal photocoagulation and vascular endothelial growth factor inhibiting agents are still undergoing various studies, yet they do appear to be effective and promising options for patients battling age related macular degeneration and diabetic retinopathy. There are reasons why a clinician may choose one over the other in hopes of achieving the maximum benefit for the patient, depending on cost, compliance, and coexisting conditions. Although vascular endothelial growth factor inhibiting agents have become the first line of defense against neovascularization and other such complications of ocular disease, there are still reasons why they may not be the appropriate treatment option for a given patient as there are associated risks. Furthermore, some clinicians believe that using alternatives such as PRP may be a better option altogether. On the other hand, an advantage of VEGF inhibiting agents over pan retinal photocoagulation is "prompt regression of neovascularization and the preservation of peripheral and night vision" (Buffolino & Park, 2019). Undergoing treatment with VEGF inhibiting medications for patients with severe vision loss may not be recommended as the drug may not be able to restore vision (Baek et al., 2019), however in most circumstances, VEGF inhibiting drugs can and perhaps should be implemented to alleviate both the visual complaints and the pathological dangers associated with chorioretinal vascular conditions. Potential risks previously discussed such as IOP elevation, inflammation, visual and pathological damage, and coexisting conditions

may need to be considered on a case by case basis, necessitating another modality of treatment. Nevertheless, it should be stressed that without a proper dilated exam, very little can be observed and treated; imaging methods can also be used to monitor the stability or progression of these diseases.

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